88. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 55 contiguous bases of SEQ ID NO:11.

89. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 70 contiguous bases of SEQ ID NO:1.

90. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 70 contiguous bases of SEQ ID NO:11. --

II. REMARKS

A. Status of the Claims:

Applicants have revised claims to include generic claims to both kappa and chimeric opioid receptor polypeptides. As discussed with the Examiner on February 4, 1998. It is hereby respectfully requested that claim directed to both kappa and chimeric opioid receptor polypeptides be examined at the present time. If it is determined that kappa embodiments will not be examined at this time, applicants request consideration of kappa elements be conducted as soon as a generic claim is allowed.

Claims 47-80 were pending in the application at the time of the Office Action. Claims 53-58, 60-62, and 68-80 are withdrawn from consideration. Claims 47-51, 59, and 63-65 stand rejection under 35 U.S.C. § 112, second paragraph, as being indefinite. Further, claims 47-51, 59, and 63-65 stand rejected under 35 U.S.C. § 112, first paragraph, as not being properly enabled. Claims 47 and 59 also stand rejected under 35 U.S.C. § 102(b) as anticipated. Claims 48-50 stand rejected under 35 U.S.C. § 103(a) as being obvious. Claims 48-50 stand rejected under 35 U.S.C. § 103(a) as obvious. Claims 52, 66, and 67 stand as objected to for being

dependent upon rejected base claims. Claims 47-52, 59, 63-67, and new claims 81-90 are now pending in the application.

B. Certified Copy of Application

A certified copy of the PCT application is being obtained for submission.

C. MPEP § 2422.02 Requirements

The Examiner objects to Figures 1,3 and 4 as not complying with the requirement of MPEP § 2422.02 that the sequence identifier be used in either the drawing or in the Brief Description of the drawing. Applicants respectfully point out that the sequence identifiers are indicated in the Figures themselves. To facilitate examination of this application, however, applicants have also amended the specification to include the sequence identifiers in the Brief Description of the Figures.

D. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 47-51, 59, and 63-65 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants have clarified claims 47-51, 59, and 63-65 to overcome these rejections.

The examiner objects to the use of the term "chimeric opioid receptor polypeptide," in claims 48 and 63, as vague. The examiner also asserts that "A chimeric polypeptide comprising an opioid receptor linked to a non-opioid receptor is not an opioid receptor. Thus, if the term

"chimeric opioid receptor" encompasses an opioid receptor linked to a non-opioid receptor, then claims 48 and 63 are improperly dependent claims.

Applicants respectfully disagree with the Examiner's characterization of the term "opioid receptor polypeptide" as vague, and characterization of claims 48 and 63 as improperly dependent. To begin, the examiner is directed to the specification at page 19, lines 7-10 where a chimeric opioid receptor polypeptide is defined as "a polypeptide that comprises amino acid sequences from two or more sources, wherein at least one of the sources is an opioid receptor polypeptide." In accordance with the specification, any chimeric opioid receptor polypeptide will include the functional aspects of the opioid receptor polypeptide. The independent claims from which claims 48 and 63 depend are drawn to a method of screening for interactivity with opioid receptor polypeptides which requires only that the functional portions of the opioid receptors be preserved in any chimera. As the independent claims reflect these aspects of the invention, claims 48 and 63 are properly-crafted dependent claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

E. Rejections Under 35 U.S.C. § 112, First Paragraph

1. Claims 47 - 51

The examiner rejects claims 47 through 51 as not reasonably enabled under 35 U.S.C. §112, first paragraph. Specifically, the examiner asserts that the specification "does not reasonably provide enablement for the diverse genus of chimeric opioid receptors encompassed by the term" because it does not provide the nucleic acid sequences encoding opioid receptors which may potentially form part of the chimeric opioid receptor.

Again, Applicants respectfully traverse. The information disclosed in the present application, in addition to general knowledge relating to the invention that is well known in the art, is more than adequate to enable one of reasonable skill in the art to construct and exploit chimeric opioid receptor polypeptides. To begin, opioid receptor polypeptides have been shown to have substantial similarities in terms of their molecular weights, function, reactivity, sequence homologies, and distribution. For example, it is known that there are at least four major classes of opioid receptors, with biochemical characterization studies from several of these groups showing a similar molecular mass of about 60,000Da, suggesting that the molecules are related. Further, the similarity of the receptor subtypes has been shown through monoclonal antibody studies showing cross-reactivity among the receptors. See Specification at pages 3-4. Additional functional similarity is evidenced by the fact that opioid receptors are G-protein-coupled receptors and therefore contain the characteristic seven transmembrane domains of G-protein-coupled receptors. See Specification at page 6, lines 30-35. Finally, opioid receptor polypeptides are largely homologous in their sequences, thus are expected to have similar three-dimensional structures.

Based on the knowledge of such substantial similarities among the opioid receptor polypeptides, it is likely that the differences observed in opioid receptors are due in part from differences in function attributable to the specific interactivity of the extracellular loops connecting the transmembrane domains. For example, the second extracellular loop of the kappa opioid receptor is interactive, as is the third extracellular loop of the delta opioid receptor, with specific ligands. Drawing on this information, it is possible to construct a chimeric polypeptide that functions as a opioid receptor polypeptide and is composed of "amino acid sequences from

two or more sources, wherein at least one of the sources is an opioid receptor polypeptide." So long as the functional domain of at least one opioid receptor polypeptide is contained in such a chimera, it will function, and may be exploited as, an opioid receptor polypeptide. This information is specifically disclosed in the application at page 18, lines 11-17, which reads as follows:

> The inventors have discovered that there are specific binding regions for each type of opioid receptor ligand. By employing a chimera that has one particular ligand binding site, for example, a kappa-specific agonist binding site, and lacks the non-specific binding site, one can screen for kappa-specific ligands without worrying about false signals from non-specific ligands.

Given this information, as well as the disclosure in the present invention of both the delta and the kappa polynucleotide sequences, the mere lack of specific polynucleotide sequences for other opioid receptor polypeptides does not prevent the manufacture of chimeric opioid receptors comprising segments from receptors other than the delta and kappa receptors. One of skill in the art can evaluate well-known information available to isolate, clone, map and combine sections of any opioid receptor polypeptides to form chimeric opioid receptor polypeptides. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 47-51 under § 112, first paragraph.

2. Claims 59, and 63-65

The examiner rejects claims 59, and 63-65 as not reasonably enabled under 35 U.S.C. §112, first paragraph. for containing "subject matter which was not described in the specification in such a way as to enable one skilled in the art . . . to make and/or use the invention." Specifically, the examiner asserts that the recited steps in claim 59, and 63-65 are not directed to

making any product; they do not enable the skilled artisan to distinguish an agonist from an antagonist of a kappa opioid receptor: and the specification does not enable the use of any opioid receptor to screen for an agonist for the kappa-opioid receptor.

Again, Applicants respectfully traverse. The claim has been amended and is now directed to a method of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor. Isolation of a specific agonist of a kappa opioid receptor is enabled in the specification as it is pointed out in the specification that agonists of opioid receptors function to inhibit cyclic AMP (cAMP) formation. This function of opioid receptor agonists is disclosed at a variety of points in the specification. For example, the examiner is directed to page 93, lines 17-20 of the specification which reads as follows:

> To investigate the functional activity of the mutant receptors, the ability of the receptors to mediate agonist inhibition of forskolin-stimulated cAMP formation is determined as described using standard techniques.

The testing of chimeric opioid receptors for their ability to mediate agonist inhibition of cAMP formation is also revealed at page 100, lines 32-34 and in the examples at page 127, lines 32-35 where it is specifically shown that kappa specific agonists inhibited cAMP accumulation.

In response to the Examiner's assertion that the specification does not enable the use of any opioid receptor to screen for an agonist with a kappa opioid receptor, the Examiner is directed to the argument set forth in response to previous rejections under § 112, first paragraph. In that argument, Applicants point out that the specification does enable the use of any opioid receptor including chimeric opioid receptors to screen for specific agonist of the kappa opioid receptor so long as the functional portions of the kappa opioid receptor are conserved in the opioid receptor utilized during the screening process. See for example, page 88 of the

specification at lines 30-35 where the results of screenings with specific selective kappa agonists and antagonists using a chimeric opioid receptor are discussed. Given this disclosure, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

F. Rejections Under 35 U.S.C. § 102

1. Rejections over Evans and Keiffer

Claim 47 is rejected as anticipated by Evan and Keiffer under 35 U.S.C. § 102(a). Evans and Keiffer disclose δ opioid receptors. The claims have been clarified to remove any claims directed to isolated δ opioid receptors. Accordingly Applicants respectfully request reconsideration and withdrawal of this rejection.

2. Rejections over Ahmed

Claims 47 and 59 are rejected under 35 U.S.C. § 102(b) as anticipated by Ahmed *et al.* Applicants respectfully traverse. For a prior art reference to anticipate, every element of the claimed invention must be identically shown in a single reference." *See, e.g. In re Bond*, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). As a matter of law, the Ahmed reference cannot anticipate the invention of claims 47 and 59.

Ahmed refers to the detection of substances which bind to an isolated kappa opioid receptor polypeptide, and to competition studies where known kappa agonists and antagonists are compared to the radiolabelled substances to determine the extent to which known agonists and antagonists inhibit radiolabelled substance binding. Ahmed does not contemplate chimeric opioid receptor polypeptides, nor does Ahmed isolate or refer in any way to the specific

sequences of the isolated kappa opioid receptor polypeptide or the polynucleotide by which it is encoded. Because these elements of the claimed invention are lacking in the cited reference, Ahmed cannot anticipate the invention of claims 47 and 59. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102.

G. Rejections Under 35 U.S.C. § 103

Claims 48-50 are rejected under 35 U.S.C. § 103(a) as rendered obvious by Evans *et al.* in view of Frielle *et al.* Specifically, the Examiner asserts that Evans "discloses a method of screening for ligands that interact with the delta opioid receptor" but "does not disclose a method of screening for ligands that interact with a chimeric delta opioid receptor." The Examiner also states that Frielle "teaches the use of chimeric β1/β2 adrenergic receptors" and that " results of the binding assay using the chimeric β-adrenergic receptor suggest that the different transmembrane regions may play a role in agonist and antagonist binding." The Examiner goes on to assert that taking these two references together renders the invention of claims 48-50 obvious. Applicants respectfully traverse.

As framed by the examiner, the rejection is improper as a matter of law. To render the chimeric opioid receptor polypeptides of claims 48-50 obvious, the cited references must:

> (1) suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and
> (2) reveal that in so making or carrying out, those of reasonable skill would have a reasonable expectation of success.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1443 (Fed. Cir. 1991) *citing In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). The present references relied upon by the Examiner

clearly fail to satisfy these requirements. Evans, in view of Frielle, does not suggest the chimeric opioid receptor polypeptides of the claimed invention, nor does it suggest that the claimed invention would be successful.

There is no teaching or suggestion in the prior art of chimeric opioid receptor polypeptides and none of the references cited by the Examiner contain evidence to the contrary. The Examiner asserts that such a teaching or suggestion may be found by combining Evans and Frielle, but this assertion is untenable. Evidence of chimeric β-adrenergic receptors and isolated opioid receptors neither teaches nor suggests chimeric opioid receptor polypeptides. Frielle's work with chimeric β-adrenergic receptors does not even mention the possibility that chimeric opioid receptor polypeptides could be similarly constructed. Further, chimeric opioid receptor polypeptides are not suggested by the study or construction of chimeric β-adrenergic receptors. Opioid receptors have fundamentally different ligand binding characteristics as compared to β-adrenergic receptors, and have dissimilar parameters for manipulation. One of skill in the art would draw nothing regarding chimeric opioid receptor polypeptides from Frielle's work. Lacking any teaching, mention, or even suggestion of them by Frielle, there cannot be an indication that chimeric opioid receptor polypeptides could be successfully constructed and useful as employed in the invention of claims 48-50.

The only location that chimeric opioid receptor polypeptides are taught is in the instant application. To draw on the information provided in the application to find a motivation for the claimed invention, or to construct an argument for rendering the claimed invention obvious, is to engage in hindsight reconstruction of the invention. The law regarding such a practice is unequivocal - the prior art, not the applicants' disclosure, must supply the requisite teachings and or

suggestions of the claimed invention. *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 312-313 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, where no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.") In this case, the prior art does not provide such information, therefore it cannot, as a matter of law, render the claimed invention obvious.

In a further note, the Examiner states that chimeric opioid receptor polypeptides could be obtained by combining portions of the delta opioid receptor with the somatostatin receptor. While that may be true, there is simply no evidence, suggestion or teaching of such a combination in the references. Such a combination is only taught in the present application. There is also nothing to indicate that such a combination would be useful for ligand binding tests or that it would even be expressed. Lacking such a teaching or suggestion in the prior art, the invention of claims 48-50 cannot be rendered obvious by the prior art.

Finally, Applicants maintain that Evans in view of Frielle teaches nothing with respect to the invention of claims 48-50. Assuming, however, that this were not the case, the cited references would actually teach away from the invention of claims 48-50. The Frielle reference refers to the use of chimeras between the β1 and β2 adrenergic receptor to identify a ligand binding domain, concluding that "subtype specificity is determined by most of the transmembrane regions of the molecule" and demonstrating that no selective, discrete region of the receptors confers selectivity of the binding adrenergic ligands. This conclusion suggests that it would not be possible to construct chimeras of the delta receptor using less than "most" of its transmembrane spanning regions. As disclosed in the instant application, however, it is the

extracellular portions of select loops of the opioid receptor polypeptides which are active in selective binding and screening for ligands. The transmembrane regions are minimally involved in selective ligand binding. If the skilled artisan were to follow the teachings of Frielle, therefore, a chimeric delta opioid receptor useful in screening for selective ligands could not be constructed.

In sum, the references cited by the Examiner do not enable, teach or suggest construction of chimeric opioid receptor polypeptides, much less suggest that such chimeric opioid polypeptides would be successful for screening purposes. To construct a *prima facie* case of obviousness, the prior art must provide, to those of skill in the relevant art, a suggestion, teaching and indication of likelihood of success of an invention. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1443 (Fed. Cir. 1991). Because the prior art does not satisfy these requirements, the Examiner has failed to make a *prima facie* case of obviousness to support the 35 U.S.C. § 103 rejections of claims 48-50. Accordingly, Applicants respectfully request reconsideration and withdrawal of these rejections.

H. Objections

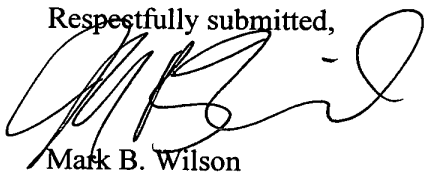
Claims 52, 66, and 67 are objected to as depending from rejected base claims. Because Applicants believe the rejections to the base claims upon which these claims depend have been overcome, claims 52, 66 and 67 are now believed to be in condition for allowance. Applicants therefore respectfully request reconsideration and withdrawal of these objections.

I. **New Claims**

New claims 81-90 have been added. These claims are directed to screening processes involving chimeric and kappa opioid receptor polypeptides, and the polynucleotides encoding for such opioid receptor polypeptides. The Examiner has not shown any teaching of any of the claimed sequences. Additionally, the amino acid sequences and nucleotide sequences of the polypeptides and polynucleotides of new claims 81-90 are acknowledged as novel sequences and have been deemed patentable subject matter in the parent application to this application (see USSN 08/292,694). Accordingly, Applicants submit that these new claims satisfy all the requirements for patentability under 35 U.S.C. and should be allowed at this time.

The Examiner is invited to contact the undersigned attorney at (512) 418-3035 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Claims Pending in USSN 08/455,683:

47. (Amended) A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) providing a opioid receptor polypeptide wherein said opioid receptor polypeptide is selected from the group consisting of: (1) chimeric opioid receptors, (2) opioid receptor polypeptides including the amino acid sequence of SEQ ID NO:2 and (3) opioid receptor polypeptides including the sequence of SEQ ID NO:12;

b) contacting said substance with the opioid receptor polypeptide; and

[b)]c) detecting [testing] the ability of said substance to interact with said opioid receptor.

48. The process according to claim 47, wherein said opioid receptor polypeptide is a chimeric opioid receptor polypeptide.

49. (Amended) The process of claim 48, wherein one [the] polypeptide of the chimeric opioid receptor polypeptide comprises the second extracellular loop of delta opioid receptor.

50. (Amended) The process of claim 48, wherein one [the] polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of delta opioid receptor.

51. (Amended) The process of claim 48, wherein the chimeric opioid receptor polypeptide comprises polypeptide portions of both kappa and delta opioid receptors.

52. The process according to claim 48, wherein said chimeric opioid receptor polypeptide is designated as $\kappa_{1\text{-}78}/\delta_{70\text{-}372}$ or $\delta_{1\text{-}69}/\kappa_{79\text{-}380}$.

59. (Amended) A process of isolating [making] a substance [product] with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

a) providing an opioid receptor polypeptide wherein said opioid receptor polypeptide is selected from the group consisting of: (1) chimeric opioid receptors, (2) opioid receptor polypeptides including the amino acid sequence of SEQ ID NO:2 and (3) opioid receptor polypeptides including the sequence of SEQ ID NO:12; [and]

b) contacting [obtaining a] said opioid receptor polypeptide with a candidate substance [specific kappa opioid receptor agonist with said opioid receptor polypeptide]; and

c) detecting [testing] the ability of said candidate substance to specifically interact as an agonist with [specific kappa opioid receptor agonist to interact with] said opioid receptor; and

d) isolating said substance [providing a product that has] if the ability to interact with the opioid receptor is detected.

63. The process of claim 59, wherein the opioid receptor polypeptide comprises a chimeric opioid receptor polypeptide.

64. (Amended) The process of claim 63, wherein one [the] polypeptide of the chimeric opioid receptor polypeptide comprises the second extracellular loop of kappa opioid receptor.

65. (Amended) The process of claim 63, wherein one [the] polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of delta opioid receptor.

66. The process of claim 63, wherein the polypeptide comprises portions of both kappa and delta opioid receptors.

67. The process of claim 63, wherein said chimeric polypeptide is designated as $\kappa_{1\text{-}78}/\delta_{70\text{-}372}$ or $\delta_{1\text{-}69}/\kappa_{79\text{-}380}$.

New Claims:

-- 81. The process according to claim 47, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide having the sequence of SEQ ID NO:2 or SEQ ID NO:12.

82. The process of claim 81, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide encoded for by the polynucleotide of SEQ ID NO: 1.

83. The process of claim 81, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide encoded for by the polynucleotide of SEQ ID NO: 11.

84. A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) providing a opioid receptor polypeptide wherein said opioid receptor polypeptide is encoded for by a polynucleotide comprising a base sequence that is identical or complementary to a segment of at least 40 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor.

85. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 40 contiguous bases of SEQ ID NO:1.

86. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 40 contiguous bases of SEQ ID NO:11.

87. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 55 contiguous bases of SEQ ID NO:1.

88. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 55 contiguous bases of SEQ ID NO:11.

89. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 70 contiguous bases of SEQ ID NO:1.

90. The process of claim 84, wherein said polynucleotide comprises a base sequence that is identical or complementary to a segment of at least 70 contiguous bases of SEQ ID NO:11. --